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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/597,608	06/20/00	NGAI J	B00-100-1

023379 HM22/0925
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EXAMINER	
TAYLOR, J	
ART UNIT	**PAPER NUMBER**
1656	4

DATE MAILED: 09/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/597,608	Applicant(s) NGAI ET AL.	
	Examiner Janell E. Taylor	Art Unit 1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *20 June 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-20, drawn to a method for normalizing and amplifying an RNA populaton, classified in class 435, subclass 6.

II. Claims 21-23, drawn to a method for making tagged driver RNA, classified in class 435, subclass 6.The inventions are distinct, each from the other because of the following reasons:

2. Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are a method for normalizing and amplifying an RNA and a method for making tagged driver RNA, which are considered separate, distinct, and capable of use without each other.

3. .Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Richard Osman on September 12, 2000, a provisional election was made without traverse to prosecute the invention of Group I, claims 1-20. Affirmation of this election must be made by applicant in replying to this Office action. Claims 21-23 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-16 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eberwine (US Patent 5,514,545) in view of Serafini (US Patent 6,114,152).

Claim 1 is drawn to a method for normalizing and amplifying an RNA population comprising the steps of: copying mRNA to form first single-stranded cDNA; converting the first ss-cDNA into first ds-cDNA; linearly amplifying the first ds-cDNA to form first amplified RNA (aRNA); tagging the 3' end of the first aRNA with a known sequence to form 3-tagged first aRNA; copying the 3'-tagged first aRNA to form second ss-cDNA; and normalizing the mRNA or the first aRNA. Claims 2-4 are drawn to normalizing the mRNA, the first aRNA, and both, respectively. Claims 5-7 are drawn to converting the second ss-cDNA to second ds-cDNA; linearly amplifying the second ds-cDNA to form

second aRNA; normalizing the second aRNA; copying the second aRNA to form third ss-cDNA; and linearly amplifying the third ds-cDNA to form third aRNA. Claims 8 and 9 are drawn to the method of tagging, comprising contacting the first aRNA with either a oligonucleotide and a ligase, or a polyadenyltransferase under conditions whereby nucleotides are added to the 3'end of the first aRNA to form the 3'-tagged first aRNA. Claims 10-12 are drawn to the converting step, which comprises contacting the first ss-cDNA with RNase H and a DNA polymerase wherein the RNase H nicks the associated mRNA and the DNA polymerase initiates conversion at non-covalently joined heteroduplex region and copies the first ss-cDNA to the first ds-cDNA, wherein the polymerase lacks or provides 5' exonuclease activity. Claims 13-15 are drawn to the mRNA copying step comprising contacting the mRNA with a primer comprising an oligo dT sequence, an RNA polymerase promoter and an affinity tag, wherein the promoter activates an RNA polymerase selected from the group consisting of T7, T3, and SP6. These polymerases are also in claim 16, which is drawn to the amplifying step. Claims 19 and 20 are drawn to a kit for normalizing and amplifying an RNA population which contains instructions of claim 1, oligo dT T7 biotinylated primer, T7 RNA polymerase, annealed biotinylated primers, streptavidin beads, polyadenyl transferase reverse transcriptase, RNase H, DNA pol I, buffers, and nucleotides.

Eberwine teaches a method for characterizing cells at the molecular level by amplifying RNA from selected single cells by microinjecting primer, nucleotides, and enzyme into acutely dissociated cells to produce amplified antisense RNA; reamplifying the amplified antisense RNA (aRNA) produced by using random hexanucleotides to

prime cDNA synthesis from aRNA, and then detecting messages in the amplified RNA. The invention is useful for characterization of cell identity or physiological state. (Abstract). In figure 2, Eberwine discloses the following: mRNA is transcribed into cDNA. cDNA is made into double-stranded cDNA. aRNA copies are made from the cDNA. cDNA copies are transcribed from aRNA copies. In regards to the step of normalizing, Eberwine teaches that "...a vast excess of driver RNA is used to hybridize all available cDNAs. The degree of hybridization is assessed by determining the amount of RNA present in double-stranded vs. single-stranded fractions as a function of time. (Col. 7, lines 30-35). Eberwine also teaches normalizing the cDNA vs. aRNA synthesis. (Col. 6, lines 1-3).

Eberwine et al. does not teach tagging of the aRNA. Eberwine also does not specifically teach "converting" the first ss-cDNA to first ds-cDNA.

Serafini et al. teach "Nucleic acids are made by adding a known nucleotide sequence to the 3' end of a first RNA having a known sequence at the 5' end to form a second RNA and reverse transcribing the second RNA to form a cDNA. In one embodiment, the first RNA is an amplified mRNA, the known sequence at the 5' end comprises a poly(T) sequence, *the adding step comprises using a polyadenyltransferase to add a poly(A) sequence to the 3' end,* the reverse transcribing step is initiated at a duplex region comprising the poly(T) sequence hybridized to the poly(A) sequence, the cDNA is converted to double-stranded cDNA by a polymerase initiating from a noncovalently joined duplex region, and the double-stranded cDNA is transcribed to form one or more third RNAs." (Abstract, Italics added.)

Serafini et al. also teach "An oligonucleotide primer, consisting of T7 RNA polymerase promoter-oligo (dT) 3', is annealed to the poly(A) tract present at the 3' end of mature mRNAs, and first-strand cDNA is synthesized using reverse transcriptase, yielding an RNA-DNA hybrid...The hybrid is treated with RNase H, DNA polymerase, and DNA ligase to convert the single-stranded cDNA into double-stranded cDNA." (Col. 4, lines 35-45).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the tagging method of Serafini with the amplification method of Eberwine. This is because the tagging method of Serafini was well known in the art at the time of the invention, and it was known that tagging aRNA was useful in the sense that the aRNA was distinguishable from other products.

It also would have been obvious to one of ordinary skill in the art at the time of the invention to use the converting method of Serafini with the amplification method of Eberwine. This is because the converting method of Serafini was well known in the art at the time of the invention, and it was well known in the art that converting ss-cDNA into ds-cDNA was useful in producing more copies of cDNA which would have then increased the amount which was to be reconverted to aRNA or detected in the solution.

5. Claims 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eberwine in view of Serafini, as applied to claims 1-16 and 19-20 above, and further in view of Gudkov et al. (US Patent 5,866,327).

Claims 17 and 18 are drawn to the normalizing step comprising hybridizing the mRNA or the first aRNA with driver polynucleotides and then separating the fraction of the mRNA or the first aRNA, wherein the separating step is effected by a method selected from the group consisting of hydroxyapatite-based affinity separation or biotin-streptavidin based affinity separation. As disclosed above, Eberwine and Serafini teach normalization.

They do not, however, teach normalization by using hydroxyapatite-based affinity separation or biotin-streptavidin based affinity separation.

Gudkov teaches "For normalization, the cDNA preparation was denatured and reannealed...The single-stranded and double-stranded DNAs from each reannealed mixture were separated by hydroxyapatite chromatography."

Gudkov does not teach the separation of aRNA or mRNA, but rather teaches the separation of cDNA for normalization purposes.

It would have been obvious, however, to one of ordinary skill in the art at the time of the invention to use hydroxyapatite chromatography with the invention of Eberwine and Serafini because affinity separation was well known in the art and used in many different applications. It would have been obvious to use it in this case because it would have been helpful in normalizing the mRNA or aRNA amounts in solution.

Summary

Claims 21-23 are withdrawn from further consideration because they are non-elected claims. Claims 1-20 are rejected under 35 U.S.C. 103(a). No claims are free of the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janell Taylor, whose telephone number is (703) 305-0273.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (703) 308-1152.

Any inquiries of a general nature relating to this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1634 via the PTO Fax Center using (703) 305-3014 or 305-4227. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Janell Taylor

September 19, 2000

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

9/21/00